Novel therapies in heart failure

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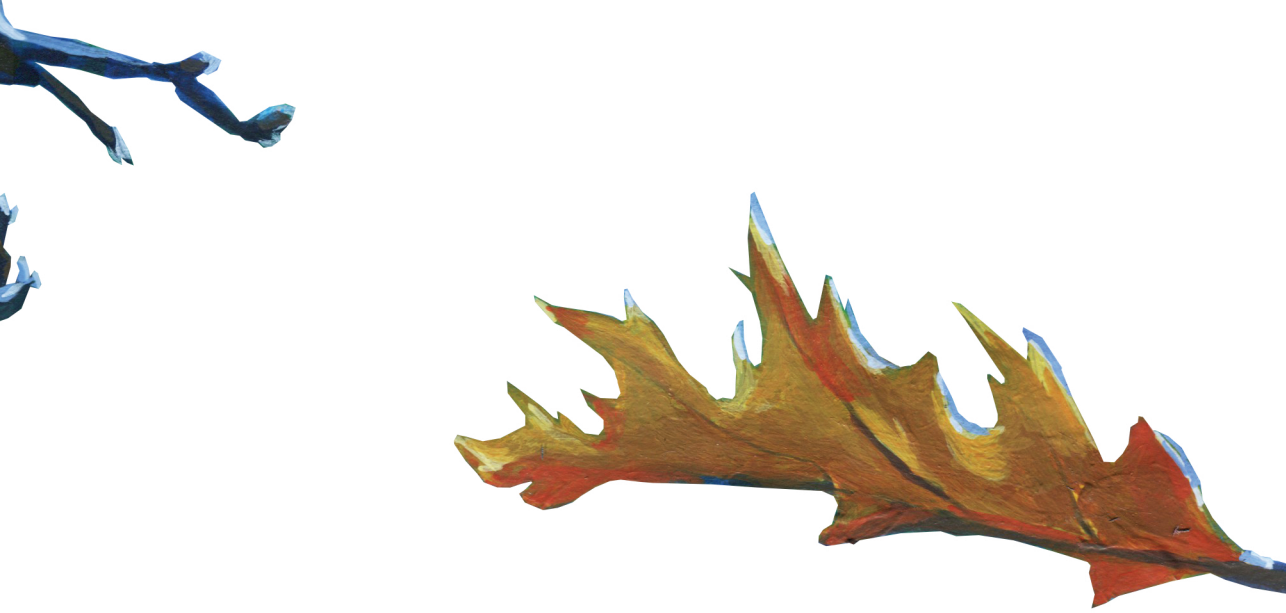

General Discussion and Future Directions

Licette C.Y. Liu

The world's population is growing and ageing. As the age of the population continues to rise, so will the incidence of heart failure. Heart failure is a serious syndrome that progressively gets worse over time and carries a dismal prognosis. Early diagnosis and treatment can however help patients to live longer and be more active. During the last decades, development of novel drugs has resulted in tremendous improvements of clinical outcome of patients with heart failure. However, this only applies to patients with heart failure and reduced ejection fraction (HFrEF). Nevertheless, despite these achievements, morbidity and mortality of patients with HFrEF remains unacceptably high. In addition, so far no drugs have shown convincingly to improve morbidity and mortality in both patients with heart failure and preserved ejection fraction (HFpEF), and patients who are admitted for acute heart failure. These observations stimulate further research on novel targets, novel therapies and novel approaches to study treatment effects.
In this thesis, we investigated novel drugs and novel approaches for the treatment of patients with HFrEF, HFpEF and acute heart failure.

PART I: PRECISION MEDICINE IN HEART FAILURE

In recent years, several clinical trials with new drugs and novel therapeutic approaches have been conducted in heart failure, but most of them yield neutral, or even negative results.[1–12] Several explanations have been addressed: wrong drugs might have been tested, wrong patients may have been included, or the wrong endpoints may have been studied. Also, the law of diminishing returns might have kicked in: improving the already significant gain by current therapy is indeed challenging. The large successes of previous studies are difficult to overcome, and trials have to include larger study populations to show a significant effectiveness of the study drug. This observation calls for an alternative approach to study treatment effect. The first part of this thesis postulates that a more personalized approach can lead to greater treatment effects and less side-effects in selected patients.

Randomized controlled trials are considered to be the 'golden standard' to study treatment effect and provide the basis of evidence based medicine, making them the dominant paradigm of current guideline recommendations. However, their results offer limited guidance when applied to individual patients. Trials are designed to select and recruit a target population and a trial is considered positive when the mean treatment effect of the study arm of the investigated drug is greater than the mean treatment effect of the study arm of the control drug. The overall treatment effect will

usually then be generalized to all patients having the disease. However, the individual treatment response may vary from exceptionally beneficial in some patients to potentially hazardous in others (Figure 1).

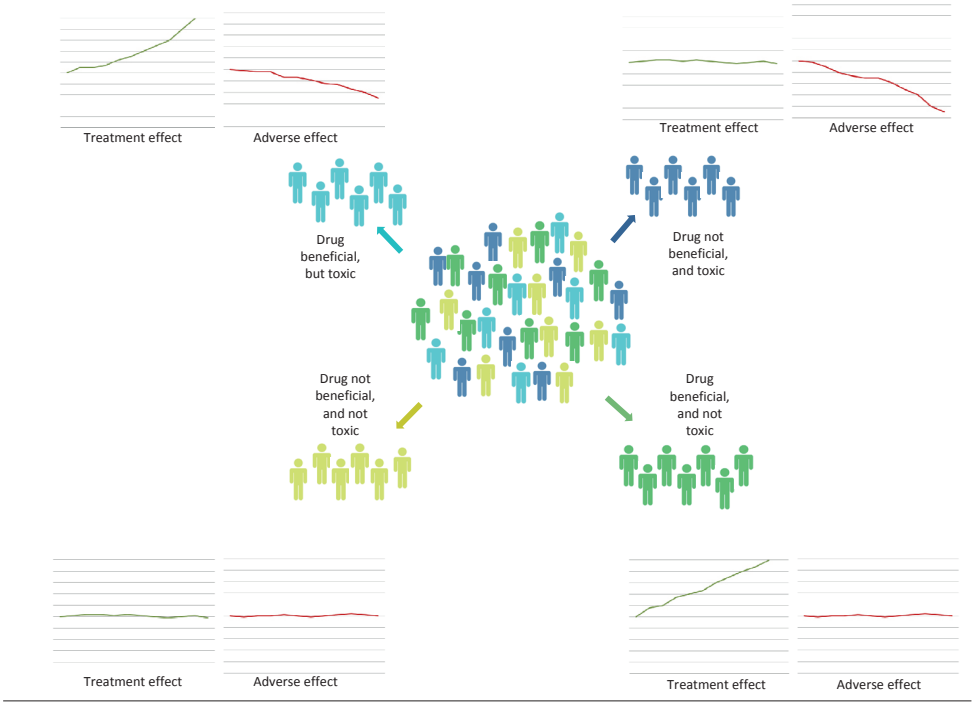

Figure 1 ● *Differential response*

Subgroups of patients can be identified based on logical biological rationale on the working mechanism of the drug. An illustrative example is the evidence showing that angiotensin-converting-enzyme (ACE) inhibitors are more effective in patients with higher plasma renin levels (indicating more activated Renin-Angiotensin-Aldosterone-System (RAAS)).[13] Another approach is to study treatment heterogeneity across subgroups. Recently, subgroups of HFpEF patients enrolled in the I-PRESERVE were identified. Overall, the I-PRESERVE showed neutral results, however in one subgroup treatment with irbesartan was associated with a decreased risk of the primary outcome (composite endpoint of death from any cause and cardiovascular rehospitalization).[14] **Chapter 1** provides an overview of approaches towards individualized treatment of heart failure. There are many examples demonstrating that treatment effects may be heterogeneous across subgroups. These subgroups may be based on clinical characteristics (such as men vs. female, young vs. old), biomarker levels or even genomic

information. Chapter 1 emphasizes the potential of these approaches, as it may assist in distinguishing responders from non-responders prior treatment, enabling physicians to provide 'precision' medicine to the individual patient.

Chapter 2 is a simple example of a differential response of a novel drug in acute heart failure amongst patients with poor and better renal function. Renal impairment is frequently found in patients with acute heart failure, and is associated with poor outcomes. Serelaxin is a novel recombinant of the naturally occurring human relaxin-2 vasoactive peptide. Evidence from rodents, healthy humans and heart failure patients suggest that relaxin may have direct beneficial impact on the kidney.[15-24] We aimed to investigate whether serelaxin mitigates the risk of renal impairment in acute heart failure patients from the RELAX-AHF trial. In addition, we aimed to study the detailed effects of serelaxin on outcomes in acute heart failure patients with renal impairment. Renal impairment was defined as an eGFR < 60 ml/min/1.73m^2. We studied the treatment effect of serelaxin in the overall study population and patients with an eGFR < 60 and ≥ 60 ml/min/1.73m^2. In the overall study population, renal impairment was associated with increased risk of cardiovascular mortality and all-cause death through day 180. In placebo treated patients, a similar risk of mortality was observed, while in the serelaxin group a trend towards an attenuated association was observed. Interestingly, the survival curves of patients with renal dysfunction treated with serelaxin, were almost comparable with the survival curves of patients with normal renal function, irrespective of their study treatment. In addition, we found a greater treatment effect of serelaxin in terms of cardiovascular mortality and all-cause death and a lower number needed to treat to prevent one cardiovascular and all-cause death in patients with renal impairment. These results emphasize that a treatment effect may be heterogeneous across a study population and that a patient's baseline risk may interact with treatment in a clinically relevant manner. This study demonstrates that subgroup analyses are important to study differential response and to reveal potential interactions between underlying pathophysiology and treatment effect. However, subgroup analyses are associated with statistical concerns. Indeed, we also hit upon these limitations in Chapter 2: the analyses unfortunately lacked power to demonstrate any significant interactions. In **Chapter 3**, we assessed treatment heterogeneity across established and novel emerging biomarkers using a novel, more accurate, robust and reliable statistical method: Subpopulation Treatment Effect Pattern Plot (STEPP).[25,26] STEPP is a novel graphical display for exploring treatment-covariate interactions and to study the magnitude of a treatment effect across the continuum of a variable[25,26] , in our case a biomarker. The aim of Chapter 3 was to identify subpopulations with distinct response to treatment using plasma biomarkers in acute heart failure. Conventional subgroup analysis based on clinical characteristics often failed to demonstrate interactions with treatment. Plasma biomarkers however may characterize individual involved

pathophysiological pathways related to individual drug responses. We studied the treatment effect of rolofylline across 48 biomarkers in acute heart failure patients from the PROTECT trial. In the overall study population, the PROTECT trial yield a neutral overall treatment effect. We found no interactions with treatment across clinical characteristics, but we found treatment interactions with several biomarkers. To identify subgroups with distinct response to treatment, we then developed a weighted score model based on biomarkers only and we used STEPP to determine a clinically relevant cut point. With this model, we identified a responding-subgroup, non-responding-subgroups and a harmed-subgroup. This study demonstrates that biomarkers may be useful in identifying subgroups with distinct treatment response, even in studies with a neutral overall treatment effect. ***Part I*** shows that a treatment effect may be heterogeneous across a study population. We showed that in positive trials or even a neutral trial there might be a group of patients with a different response (i.e. greater treatment effect, or even experiencing a harmful effect). Instead of the one-size-fits-all treatment recommendation, understanding treatment interactions are thus necessary to identify those patients who are likely to benefit from treatment and is an essential first step towards much needed personalized treatment strategies in heart failure. Future drug development programs could benefit from such information in order to match the right patient to the right drug.

PART II: NOVEL DRUGS FOR THE TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

Over recent decades, heart failure therapy has improved. However, this accounts only for the treatment of HFrEF. The incidence of HFpEF is increasing and current prevalence counts up for more than 50% of all heart failure cases.[27,28] Unfortunately, to date, no treatment has yet been shown to improve morbidity and mortality of HFpEF.[29] Therefore, a high urge exists for novel effective drugs for patients with HFpEF in particular.

When the heart fails, the RAAS becomes active to preserve cardiac output. However, on long term, this system can become maladaptive. Inhibiting the RAAS by ACE-inhibitors, angiotensin II receptor antagonists, and aldosterone receptor blockers, is therefore the cornerstone of heart failure therapy. An alternative route to inhibit the RAAS is by the prevention of degradation of natriuretic peptides.[30] Natriuretic peptides cause RAAS inhibition by reducing plasma renin levels and inhibiting angiotensin II-stimulated aldosterone release. Other cardiovascular effects of natriuretic peptides are altering vascular tone and fluid balance, resulting in a reduction

in blood pressure. Also, natriuretic peptides stimulate diuresis, natriuresis, reduce sympathic tone to peripheral tissue and have anti mitogenic activity. Neprilysin, also known as a neutral endopeptidase 24.11 (NEP) is a zinc-containing, membrane-bound extracellular metalloprotease that cleaves many vasoactive peptides, including natriuretic peptides (atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-natriuretic peptide (CNP)), but also bradykinin, endothelin-1, adrenomedullin, and angiotensin II.[31–33] N-terminal prohormone of brain natriuretic peptide (NT-proBNP) however, is not degraded by NEP.[34] By inhibiting NEP, cleaving of natriuretic peptides is prevented, which would result in decreased RAAS activity. Clinical trials with NEP inhibitors have failed to show significant reduction in blood pressure, despite elevated ANP levels.[35] In fact, in one study including hypertensive patients, treatment with a NEP inhibitor increased ANP levels which lowered blood pressure, but under an increased renin-angiotensin and sympathetic activity condition.[36] Therefore, it was suggested that concomitant inhibition of NEP and ACE would produce a consistent lowering of blood pressure.[35] Indeed, animal studies have shown that treatment with inhibitors of ACE and NEP combined resulted in a more pronounced reduction in blood pressure, compared to the effect when each enzyme inhibitor was studied separately [37,38]. However, clinical trials with compounds inhibiting both ACE and NEP reported an increased incidence of angio-oedema (0.73%), compared with ACE-inhibitors (0.1-0.5%)[35]. The precise mechanism of this drug-induced angio-oedema remains unknown, however it is likely that the accumulation of bradykinin secondary to both ACE and NEP inhibition may play a role. [31,35] The relatively high incidence of angio-oedema discontinued the development of combined ACE and NEP inhibition in one compound.[31] Thus, other approaches to inhibit RAAS and NEP dually where explored. LCZ696 is a novel dual-acting angiotensin receptor-neprisylin inhibitor (ARNi), and compromises the angiotensin II AT1 receptor antagonist valsartan and the neprilysin inhibitor prodrug AHU377 in one compound.[39] A large outcomes trial in HFrEF recently showed that LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization.[40] The PARAMOUNT investigated the safety and efficacy of LCZ696, compared with valsartan in HFpEF.[41] Treatment with LCZ696 resulted in a greater reduction of NTproBNP compared with the valsartan group. Further, signs indicating reverse atrial remodeling and improvement of NYHA functional class were also noticed in patients on LCZ696. In **Chapter 4**, we studied the effects of LCZ696 on renal function in patients with HFpEF, compared with valsartan. Since LCZ696 blocks the action of angiotensin II and elevates biologically active natriuretic peptides, bradykinin, and adrenomedullin it is expected that LCZ696 might have different effects on renal function, compared with the renal effects of RAAS inhibiting agents. In addition, RAAS inhibiting induced worsening renal function is not necessarily related to worse outcomes in patients with HFrEF, but in HFpEF it is shown to be associated

with increased risk.[42–44] We studied the effect of LCZ696 on serum creatinine, eGFR, cystatin C, urine albumin creatinine ratio and worsening of renal function in 301 patients with HFpEF after 12 and 36 weeks of treatment. Worsening renal function (WRF) was determined as a serum creatinine increase of >0.3 mg/dL and/or >25% between two time-points. At baseline, there was no difference in mean eGFR between in the LCZ696 group and valsartan group. We observed a more pronounced blood pressure decrease in patients treated with LCZ696, compared with valsartan at both week 12 and 36. The eGFR declined less in the LCZ696 group than in the valsartan group. The incidence of WRF was lower in the LCZ696 group than in the valsartan group at any time-point, but this difference was not statistically significant. Over 36 weeks, the geometric mean of UACR increased in the LCZ696 group, whereas it remained stable in the valsartan group. We demonstrated that treatment with LCZ696 was associated with preservation of eGFR compared with valsartan, but an increase in albumin creatinine ratio. This study suggest that LCZ696 may attenuate decline in renal function in patients with heart failure with preserved ejection fraction. However, further, larger studies are needed to confirm the beneficial effect on glomerular function, but deterioration of urine albumin creatinin ratio of LCZ696 and whether this will impact outcomes in patients with HFpEF.

A significant portion of patients with HFpEF develop pulmonary hypertension.[45] Wide ranges of incidence and prevalence have been reported, mainly due to differences in cut-off points, parameters used and the method of diagnosing.[46] Patients with HFpEF and concomitant pulmonary hypertension experience severe symptoms and have worse outcomes. The complex interplay of pathophysiological mechanisms associated with the development of HFpEF result in passive backward transmission of left sided filling pressures.[47,48] This results in longstanding pulmonary venous congestion.[46,49,50] In this condition, PAP and PAWP are elevated, while the transpulmonary gradient (TPG), diastolic pulmonary gradient (DPG) and pulmonal vascular resistance remain normal. This stage is classified as isolated post-capillary pulmonary hypertension.[46,49] For reasons yet unknown, some patients also develop pre-capillary pulmonary hypertension resulting in elevated TPG, DPG, and pulmonary vascular resistance.[46,49,50] These patients have combined post-capillary and pre-capillary pulmonary hypertension.[46,49,50] It should be noted however that HFpEF patients may also have a pre-capillary component due to other co-morbidities. Eventually, increased pulmonary pressures may cause an increased the right ventricular (RV) afterload, resulting in RV failure.[51,52] Treating pulmonary hypertension in HFpEF has therefore become of interest as a target of therapy. The nitric oxide (NO) system plays a central role in the regulation of vascular tone of the systemic and pulmonary vasculature. Sildenafil, a potent PDE-5 inhibitor, selectively reduces pulmonary vascular resistance by nitric

oxide (NO) mediated vasodilatation.[53,54] and is one of the first choice regimens for the treatment of pulmonary arterial hypertension (PAH).[49,53,55,56] Pre-clinical studies also suggested that PDE-inhibition exerted cardiac protective, anti-hypertrophic and anti-remodeling effects.[57,58] It was therefore hypothesized that treatment with sildenafil results in beneficial outcomes in patients with HFpEF and concomitant pulmonary hypertension. Even though the evidence for this indication was limited, sildenafil is currently often prescribed to patients with HFpEF and pulmonary hypertension. Only two studies have investigated the effect of sildenafil in patients with HFpEF, and both show contrary results.[59,60]

In **Chapter 5**, we studied the effects of sildenafil on invasive hemodynamics and exercise capacity in patients with HFpEF and pulmonary hypertension. We included 52 patients with HFpEF (LVEF ≥ 45%, NYHA II-IV) and pulmonary hypertension (invasively measured mean PAP ≥ 25 mm Hg and PAWP ≥ 15 mm Hg). Eligible patients were randomized in a 1:1 ratio to sildenafil (60 mg t.i.d.) or matching placebo and treated for 12 weeks. After 12 weeks of treatment, sildenafil did not result in benefical effects on mean PAP, mean PAWP, cardiac output and exercise capacity, compared with placebo. In **Chapter 6**, we investigated more detailed effects of sildenafil on additional outcomes, including cardiac structure and function, biomarkers, parameters of cardiopulmonary exercise testing and health-related quality of life measures. After 12 weeks of treatment with sildenafil, there were no beneficial effects of sildenafil on cardiac structure and function, exercise capacity, biomarkers and quality of life, compared with placebo. Several explanations for this lack of effect have been addressed: based on a biological pathophysiological rationale, pulmonary hypertension may be a sign of advanced stage of HFpEF, thus it may have been difficult for any treatment to have an impact. Also, based on logical biological rationale, the effects of sildenafil may only have major impact in HFpEF and pulmonary hypertension patients, who have significant pre-capillary component pulmonary hypertension.[61] We have however screened patients from a broad population of HFpEF patients with high likelihood of pulmonary hypertension throughout several years and our study population had predominantly post-capillary pulmonary hypertension, whereas a small portion of patients had combined post- and pre-capillary pulmonary hypertension[62]. This observation suggest that the incidence of HFpEF patients with pulmonary hypertension with significant pre-capillary pulmonary hypertension among already severe symptomatic HFpEF patients is rather low. Our results do not support the use of sildenafil in patients with HFpEF and pulmomary hypertension. However, as our study population were predominantly patients with post-capillary pulmonary hypertension, the role of sildenafil in patients with both post- and pre-capillary pulmonary hypertension remains to be evaluated.

PART III: DRUG EVALUATIONS OF NOVEL DRUGS FOR THE TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION

In the final part of this thesis, two drug evaluations are provided in **Chapter 7** and **Chapter 8**. **Chapter 7** is a review of finerenone, a novel nonsteroidal mineralocorticoid receptor antagonist. Mineralocorticoid receptor antagonists (MRA) have been shown to reduce the risk of hospitalization and mortality in heart failure.[63,64] To date, two steroidal MRA are developed for the treatment of heart failure: spironolactone and eplerenone. Despite the evidence for their treatment benefit, their use is limited due to characteristics side effects. Spironolactone is highly potent, but is structurally similar to progesterone, resulting to side effects such as gynecomastia and impotence.[65,66] Eplerenone has improved selectivity but a relatively low affinity. Other important adverse effects is the increased risk of elevated potassium levels or hyperkalemia and worsening of renal function.[66–68] These limitations have stimulated further development of a novel MRA without these side effects. Finerenone is a novel nonsteroidal MRA, with higher selectivity toward the mineralocorticoid receptor (MR) compared to spironolactone and stronger MR-binding affinity than eplerenone.[69] In addition, finerenone is equally distributed into cardiac and renal tissues, in contrast to spironolactone and eplerenone, which have 3 to 6 fold increased concentration in renal tissue compared with cardiac tissue. It is therefore thought that administration of finerenone is associated with lower risk of hyperkalemia and worsening renal function, as lower doses are needed (due to increased selectivity and affinity) and because of the equal distribution in cardiac and renal tissues. The first results of finerenone in heart failure patients and patients with diabetic kidney disease are encouraging, but need to be confirmed by further studies investigating whether the beneficial effects of finerenone translate into improved clinical outcomes.

Chapter 8 is a review of omecamtiv mecarbil, a novel small-molecule, selective, cardiac myosin activator. Decreased cardiac contractility is the central feature of systolic heart failure, but the cornerstones of current heart failure therapy are not agents that improve cardiac contractility. Current available drugs that improve cardiac function (i.e. inotropes) are associated with serious adverse effects such as ischemia, arrhythmias and mortality[2,4,70–74], and these adverse effects stimulated further development of a novel drug with improving cardiac contractility as a target. Omecamtiv mecarbil accelerates the transition from the weakly bound to the strongly bound state, enabling more myosin heads to enter the force-generating state.[75] As a result, systolic ejection time increases and cardiac contractility improves. The first results of omecamitiv mecarbil in healthy humans, chronic systolic heart failure and acute heart failure show promising results. Treatment with omecamtiv mecarbil increased systolic ejection time, systolic ejection fraction, fractional shortening, stroke volume, and NT-proBNP

levels. However, increased levels of troponin were observed in patients receiving higher doses of omecamtiv mecarbil, thus an important adverse effect may be dose-related myocardial ischemia. Further studies are therefore needed to investigate whether the beneficial effects of omecamtiv mecarbil translate into improved clinical outcomes.

FUTURE PERSPECTIVES

The treatment of patients with heart failure has markedly improved over the past decades, but the field needs to evolve further. Failure of the development of novel effective treatments calls for better insights in important pathophysiolocial mechanisms and identification of potential targets. However, to simply discover novel drug targets might not be enough. It seems that the large treatment benefits that were seen in the first trials are successes of the past. Over the last years, many trials with potential novel drugs have yield neutral results, indicating that improving the already significant gain is challenging. In addition, polypharmacy may also influence therapeutic compliance. As a result, future clinical trials should include larger study populations to observe a significant difference in treatment effect. This is undesirable, expensive and time-consuming. Alternative approaches are therefore needed to improve therapy of heart failure.

Polypharmacy could be addressed by a polypill, combining multiple active pharmaceutical ingredients in one compound. However, to improve the already significant gain of current treatment, we have to look at patients. Between heart failure patients there are many differences: differences in characteristics, etiology and co-morbidity. These inter-individual differences in heart failure hold great potential for precision medicine. The fundamental principle behind precision medicine is to identify certain patient profiles, characterized by clinical characteristics, biomarkers, metabolomics, transcriptomics or even genetic information, that are associated with a distinct response to treatment. Tailoring treatment will result in the greatest treatment benefit while reducing the risk of adverse effects. Although the cardiology field might hold great potential for precision medicine, there are many hurdles that have to be overcome before this approach can be implemented. The first step would be retrospective analysis of data of previous conducted phase II trials to explore potential subgroups with specific signatures which have a distinct treatment response. However, some datasets are lost, not available or have minimal information regarding biomarkers and genetic information, making it impossible to study treatment heterogeneity across these variables. Future phase II trials should therefore include broader and large study populations, and additional biomarkers or genetic information related to underlying

biological components should be collected and studied. Analyzing such big data is challenging. In fact, it may not be easy: a phenotype may not reflect underlying biological mechanisms related to differential response and a single gene contributes only to a small amount of information. One example regarding the difficulties to identify a target subgroup based on one phenotype characteristic comes from the results of the PRAISE trials studying the effect of amlodipine in heart failure patients. The first PRAISE trial was a hypothesis generating trial including patients with ischemic cardiomyopathy and nonischemic dilated cardiomyopathy. Subgroups were pre-specified and patients were allocated to amlodipine or placebo on separate strata. After a mean follow-up of 13.8 months, there was a significant treatment interaction across the etiology of heart failure. Among patients with ischemic cardiomyopathy, treatment with amlodipine did not result in a reduced risk of cardiovascular morbidity and all-cause mortality (HR 1.04, 95% CI 0.83-1.29, p = ns), while among patients with nonischemic dilated cardiomyopathy treatment with amlodipine resulted in reduction in risk of cardiovascular morbidity and all-cause mortality (HR 0.69, 95% CI 0.49-0.98, p = 0.04).[77] The investigators should be complemented that they thus designed the definitive PRAISE 2 trial, including only patients with heart failure with nonischemic dilated cardiomyopathy.[78] Unfortunately, after a median follow-up time of 33 months, treatment with amlodipine did not result in a reduced risk of all-cause mortality, cardiovascular death and rehositalizations. These results of the PRAISE trials demonstrate the difficulties of only using a baseline characteristic to target therapy. Apparently, there are multiple factors influencing response to treatment. Systems biology is an emerging holistic approach that focus on complex interactions within biological systems and is based on the concept that all systems (proteins and genes) act together in concert. Systems biology studies the complexity of systems over time and under varying conditions, and demands a collaboration of many scientific disciplines: medical science, biology, bioinformatics, computer science, and engineering. Because of the ability to study everything in concert, systems biology may reveal biological elements which determine the expression and appearance of health and disease, and factors underlying pathophysiological pathways associated with treatment response. Systems biology may therefore overcome the limitations related to identifying a subgroup based on one patient characteristic. In addition, as traditional subgroup analyses are often associated with statistical concerns, novel statistical methods and analytic approaches need to be developed and implemented. Gathered information regarding differential response should then be taken into account in the trial design of phase III trials. Study inclusion and exclusion criteria should characterize the responder population of the investigated drug, thereby increasing the likelihood of future trial success. The next step is to develop an easy, simple, inexpensive tool to identify responders and non-responders, enabling physicians to distinguish responders from non-responders

prior treatment. For example, this could be a responder risk score based on variables with treatment interaction, or a set of biomarkers, transcriptomics, metabolomics or even genetic blueprint (Figure 2).

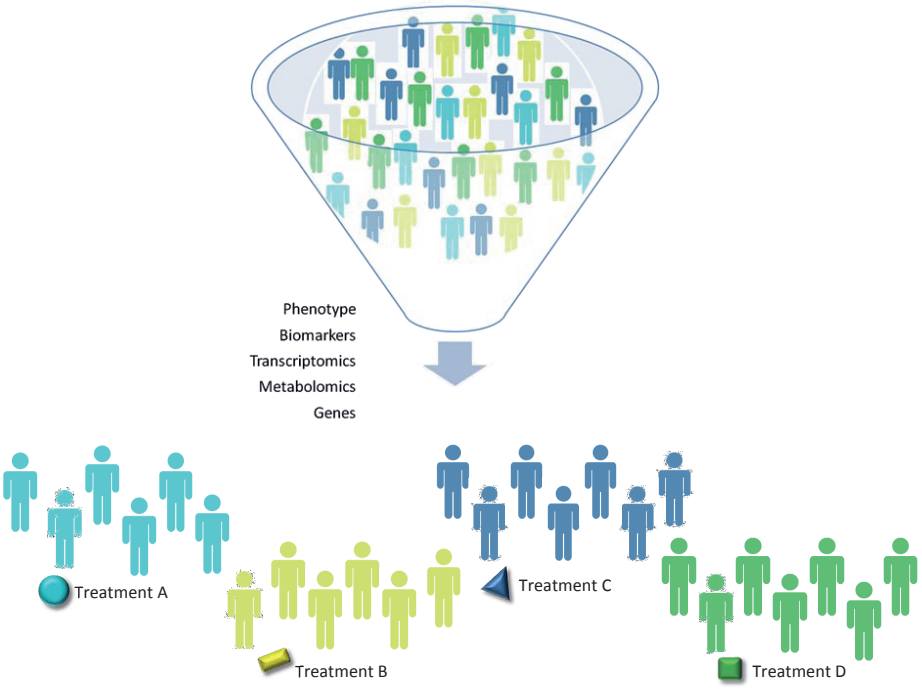

Figure 2 ● Tailoring treatment

Taken together, precision medicine in cardiology may sound like a long shot. However, along with increasing understanding of the basis of disease heterogeneity, development of powerful methods for characterizing patients (proteomics, metabolomics), technological innovations in genome research, and the ability to analyze large datasets with state-of-the art statistical methods, the distance to a breakthrough may be closer than it seems. There are already a few ongoing trials that have been designed considering the underlying working mechanism of the drug. The ACTIVATE trial for instance investigates tolvaptan, an arginine vasopressine antagonist (AVP) in patients with high copeptin levels, as copeptin is the C-terminal portion of pro-AVP, mirroring AVP levels. (ACTIVATE, NCT01733134). In addition, the RELAX-AHF trials[76] included acute heart failure patients with a systolic blood pressure of 125 mm Hg or higher. As serelaxin is a vasodilatator it is indeed expected to be safer en probably more effective in patients with high blood pressures (RELAX-AHF-2 NCT01870778).

To overcome the barriers of precision medicine different stakeholders involved in precision medicine should embrace actions. Reseachers and biotechnology companies should move R&D of biomarkers towards companion diagnostics (tests to identify patient's likelihood of response or risk of experiencing harmful effects). Currently, up to 50% of drugs in development have an associated biomarker program. This number should (and hopefully will) increase over time. Physicians should also embrace the effect of performing diagnostic tests. Some tests may be in favor of physician economics, while other test may hurt physician economics. For example, some diagnostic tests will reveal patients at higher risk who should be seen more often by the cardiologist, while other diagnostic tests will identify patients who do not need therapy, resulting in a decline in administration of the drug, thus diminishing billing fees. In addition, pharma should face the risk that some drugs may have a decline in the market share as these agents may not be applicable in the broader population, while embracing the potential that other drugs will capture value through identification of responders. Together, researchers, physicians, but also the industry should have a greater willingness to accept results and information regarding treatment heterogeneity, and important signals should be taken into account in the design of future trials. In addition, even if future developments overcome abovementioned key scientific and economic hurdles, there are also challenges related to operational issues, such as issues regarding privacy concerns, that should be addressed. These challenges demand ethical and legal frameworks that can only be established by the involvement of medical professionals, patients, governments, and policy makers.

Segmentation of population into subgroups will not only change the dynamic of drug development but also clinical practice. Direct selection of optimal therapy, will increase treatment benefit, avoid adverse effects, increase patients compliance to treatment, reduce trial-and-error-prescription, and eventually control overall health care costs. Therapies should be tailored to specific heart failure phenotypes and/or genotypes with distinct response to treatment. Future trials should be designed taking differences in characteristics of patients, such as genetic background, associated pathophysiological processes, plasma biomarker status or non-cardiac co-morbidities, into account. Only if novel therapeutic concepts and future clinical trials integrate these different aspects of patients we can improve the management of heart failure.

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